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AEROSOLIZED AZOLE ANTIFUNGALS

[57] Abstract
There are described pharmaceutical formulations comprising as active ingredient, an azole antifungal in a form suitable for administration by inhalation. Such formulations include pressurised aerosol formulations, non-pressurised aerosol formulations and solutions/suspensions for use with a nebuliser device. Also described is finely divided powdered azole antifungal with a mass median diameter in the range 0.1 to 10 microns and a method of prophylaxis of a fungal pulmonary infection which comprises administering by

inhalation a therapeutically effective amount of an azole antifungal to a patient predisposed to such an infection.

Detailed Description

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Aerosolized Azole Antifungals

This invention relates to novel pharmaceutical formulations and a novel therapeutic method of using them.

Invasive fungal infections cause significant morbidity and mortality especially in patients with impaired immune defenses. Because of the increasing number of immunocompromised patients due to organ transplantation, chemotherapy and AIDS, control of fungal infection is now a major health issue.

In recent years. the development of the azole group of antifungal agents has contributed greatly to the treament of fungal infections.. Such compounds are normally administered in suitable formulations orally, topically to the skin, or by pessary or suppository. When administered by such routes, however, even the potent azole antifungal agents have little or no effect on an established, invasive fungal infection of the lung of an immunocompromised patient.

We have now found that administration of an aerosolised formulation of a suitable azole antifungal agent to the lungs of immunocompromised patients prevents or greatly inhibits the onset of fungal disease.

According to the invention we provide a pharmaceutical formulation comprising, as active ingredient, an azole antifungal in a form suitable for administration by inhalation.

The prophylactic administration of azole antifungal agents to the lung will be particularly effective in the prevention of fungal infections whose main portal of entry

is the respiratory system, especially those caused by asDercillus and cryptococcus species. In addition, use of low doses applied directly to the lungs will minimise the risks of the side effects seen with systemic antifungal agents.

By azole antifungal agents we mean those having an imidazole (structure I, X CH) or triazole (structure I, X N) moiety.

Particular azole antifungal agents which may be mentioned are, for example, clotrimazole, econazole nitrate, fluconazole, itraconazole, ketoconazole, miconazole nitrate and saperconazole.

Forms suitable for administration by inhalation include aqueous solutions/suspensions, for use with a nebuliser device; dry powder and pressurised dry powder aerosol.

Suitable nebuliser solutions/suspensions may be prepared by adding the azole antifungal agent to water, which has preferably been distilled or sterilised. If necessary or desired the aqueous medium may include suspending agents, solubilising agents, stabilisers and/or preservatives. The formulation may additionally contain another prophylactic agent, such as pentamidine, or a bronchodilator.

For inhalation as a powder formulation the active ingredients in finely divided form may be used in admixture with a larger sized carrier comprising particles, eg of up to 400 microns diameter. We prefer at least 90% by weight of the particles of the carrier to have an effective particle size below 400 microns, and at least 50% by weight of the particles of the carrier to have an effective particle size above 30 microns. Effective particle size for particles below 30 microns may be measured by a Coulter counter. Effective particle size for particles above 30 microns may be measured by an Alpine air jet sieve.

Desirably, at least 95% by weight of the particles of

the active ingredients have an effective particle size in the range 0.1 to 10 microns. Preferably at least 90% and more desirably at least 95% by weight thereof.have an effective particle size in the range 1 to 10 microns. Suitably at least 50% by weight of the particles of the active ingredients have an effective particle size in the

range 1 to 5 microns.

The particle size spectrum of the carrier will depend on the particular inhalation device from which the formulation is to be dispersed. It is however desirable to avoid carrier particles of less than 10 microns in size, thus minimising the number of non-drug particles which penetrate deep into the lung. A large proportion of very large particles may also cause a gritty feel in the mouth of the user and is therefore less preferred. Use of a carrier of large particle size may also cause problems in filling when using filling machines which involve a dosator which picks up powder by dipping into a powder bed from above. However, use of a carrier of large particle size may ease filling when using machines in which a die is filled from above, but may incline the composition to segregate during transport or storage. Thus , desirably, at least 95% by weight of the particles of the carrier have an effective particle size below 400 microns. Preferably at least 50%, and more desirably at least 70%, by weight of the carrier particles have an effective particle size in the range 30 to 150, especially 30 to 80 microns.

The composition preferably contains from 2 to 50% by weight, more especially from 5 to 25% by weight and particularly from 10 to 15% by weight of the active ingredient, and from 50 to 98% by weight, more especially from 75 to 95% by weight and particularly from 85 to 90% by weight of the carrier.

The finely divided active ingredients may be prepared in the desired particle size range for example using a ball mill, a fluid energy mill, by precipitation or by spray drying. The carrier may be prepared by spray drying or grinding and subsequently separating out the desired fraction, for example by air classification and/or seiving.

Spray dry separately.

The powder compositions may be prepared by mixing the ingredients together in one or, preferably, more (eg two) steps in a mixer, such as a planetary or other stirred mixer.

The carrier may be any non-toxic material which is chemically inert to the active ingredients and is acceptable for inhalation. Examples of carriers which may be used include inorganic salts, eg sodium chloride or calcium carbonate; organic salts, eg sodium tartrate or

calcium lactate; organic compounds, eg urea or propylidone; monosaccharides, eg lactose, mannitol, arabinose or

0 dextrose monohydrate; disaccharides, eg maltose or sucrose; polysaccharides, eg starches, dextrins or dextrans. A particularly preferred carrier is lactose, eg crystalline lactose.

The powder compositions will generally be put in

5 sealed gelatine, plastic or other capsules. The container is preferably loosely filled to less than about 80% by volume, preferably less than about 50* by volume with the powder composition.

Alternatively, for inhalation the active ingredients may be used in pellet or granule form, wherein the pellet or granule is soft, is from 10 to 1,000, preferably from 30 to 500 microns in diameter and comprises an agglomeration of individual medicament particles, at least 90% by weight of which have a diameter of less than 10 microns.

The soft pellet or granule preferably has an internal coherence.such that the pellet or granule remains intact when filled into a container, eg a capsule, using automatic or semi-automatic filling machines, under conditions of transport and storage, and when fluidised within a

.5container in the device from which it is intended to dispense the pellets or granules and yet may be broken up into particles of a therapeutically effective size outside the container as it discharges from the container.

We have found that satisfactory soft pellets or

0 granules for use in insufflators of the type described in British Patent No. 1,182,779 (commercially available under the Registered Trade Mark 11Spinhalerll) and powdered by human inhalation have a mean size in the range of from 50 to 250 microns, preferably a mean size in the range 120 to

5160 microns and most preferably a mean size of about 140 microns.

For pressurised aerosol formulations, the active ingredients are preferably finely divided, eg at least 95* by weight of the paticles of the active ingredient have an effective particle size of from 1 to 10 microns (and these finely divided forms of the active ingredients are a feature of the invention). We particularly prefer the

active ingredient to have a mass median diameter of less than 5 microns and especially of less than 4 microns and most preferably of less than 3.5 microns. we also prefer not more than 5% by weight of the particles to have a diameter of greater than 10 microns, and more preferably not less than 90% by weight of the particles to have a diameter of less than 6 microns.

We prefer the composition to contain from 0.1 to 12%, more preferably from 0.2 to 5%, eg about 1 to 3.5% by weight of the finely divided active ingredients.

By mass median diameter we mean the diameter such that half the particulate mass is in particles of lesser diameter and half in particles of greater diameter. The mass median diameter is essentially a Stokes diameter and may be determined using a Joyce Loebl sedimentation disc centrifuge either in a two layer or line start photometric mode (Bagness i and Ottaway A, Proc. Soc. Analyt. Chem. 2_5 Part 4, Vol 9, 1972 pages 83 -86) .

The active ingredients of mass median diameter less than 4 microns when formulated as aerosol units and when the units are examined using a single stage liquid impinger (modification of that described in J. Pharm. Pharmac. 1973, 25, Suppl. 32P-36P) produce a greater dispersion than exactly analogous units containing active ingredients of larger mass median diameter. The single stage liquid impinger samples the whole cloud delivered from the aerosol and separates it into two fractions by inertial impaction.

The fraction of smaller particle size is less than 10 microns in aerodynamic diameter and represents material which is likely to penetrate into the deeper regions of the human airways.

By providing a large proportion of fine particles of active ingredient the invention enables effective lung penetration to potential sites of organism colonisation.

The fine active ingredient(s) may be made by grinding or milling and is (are) preferably dried thoroughly before they are incorporated into the liquefied propellant medium.

The liquefied propellant is preferably a gas at room temperature (20OC) and atmospheric pressure ie it should have a boiling point below 200C at atmospheric pressure. The liquefied propellant should also be non-toxic. Among the suitable liquefied propellants which may be employed

5 are dimethyl ether and alkanes containing up to 5 carbon atoms, eg butane or pentane, or a lower alkyl chloride, eg methyl, ethyl or propyl chlorides. The most suitable liquefied propellants are the fluorinated and fluorochlorinated lower alkanes such as those sold under

5 the Registerd Trade Mark 11Freonll. Mixtures of the above

mentioned propellants may be suitably employed. Examples of these propellants are:

dichlorodifluoromethane ("Propellant 1211);

1,2-dichlorotetrafluoroethane (UPropellant 11411);

0 trichloromonofluoromethane (OPropellant 1111);

dichloromonofluoromethane ("Propellant 2111);

monochlorodifluoromethane ("Propellant 2211);

trichlorotrifluoroethane (OPropellant 11311);

monochlorotrifluoromethane ("Propellant 1311).

L5 asymmetric dihydrotetrafluoroethane ("Propellant 134all)

Propellants with improved vapour pressure characteristics may be obtained by using certain mixtures of these compounds, eg "Propellant 1111 with 0Propellant 1211 or

20"Propellant 1211 with "Propellant 11411. For example, "Propellant 1211, which has a vapour pressure of about 570kPa (absolute) at 200C, may be mixed in various proportions to form a propellant having a desired intermediate vapour pressure. We prefer compositions which

25do not contain trichloromonofluoromethane. It is desirable that the vapour pressure of the propellant employed be between 380 and 500, and preferably between 410 and 470kPa (absolute) at 200C. Such a propellant mixture is usable safely with metallic containers. other mixtures of "Propellant 1211 with "Propellant 11411, or of "Propellant 1211 with "Propellant 1119, or of "Propellant 1211 with "Propellant 1111 and "Propellant 11411 with absolute vapour pressures at 200C in the range 230 to 380kPa are usable safely with

0 reinforced-glass containers.

The composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-iohic surface active agent or may be a solid anionic surface active agent.

5 The preferred solid anionic surface active agent is sodium dioctylsulphosuccinate.

The amount of the surface active agent required is related to the solids content of the suspension and to the

particle size of the solids. In general it is only

0 necessary to use 5-15%, and preferably 5-8% of the solid surface active agent by weight of the solids content of the suspension.

When a liquid non-ionic surface active agent is employed it should have an hydrophile-lipophile balance

5ffiLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface active properties of a surface active agent. The lower the HLB ratio, the more lipophilic is the agent and, conversely, the higher the HLB ratio, the more hydrophilic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W C Griffin in the Journal of the Society of Cosmetic Chemists, Vol 1, No 5, pages 311-326 (1949). Preferably the surface active agent employed should have an HLB ratio of 1 to 5. It is possible to employ mixtures of surface active agents, the mixture having an HLB ratio within the prescribed range.

Those surface active agents which are soluble or dispersible in the propellant are effective. The more propellant soluble surface active agents are the most effective.

We prefer the liquid non-ionic surface active agent to comprise from 0.1 to 2%, and more preferably from 0.2 to 1% by weight of the total composition. Such compositions tend to be more physically stable on storage.

Among the liquid non-ionic surface active agents which may be employed are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, oleostearic and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the Registered Trade Mark "span") and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides, may be employed. The preferred liquid non-ionic surface active agents are the oleates of sorbitan, eg those sold under the Registered

Trade Marks'llArlacel V' (sorbitan sesquioleate), "Span 8011 . 1

(sorbitan monooleate) and "Span 8511 (Sorbitan trioleate). Specific examples of other liquid non-ionic surface active agents which may be employed are sorbitan monolaurate, polyoxyethylene sorbitol tetraoleate, polyoxyethylene

5sorbitol pentaoleate and polyoxypropylene mannitol dioleate. A solid non-ionic surface active agent which may be mentioned is lecithin, eg soya lecithin, a vegetable lecithin extracted from soya beans, but lecithin is not preferred.

0 We particularly prefer compositions containing a sorbitan or sorbitol ester, eg sorbitan trioleate in a mixture of propellants 12 and 114. We prefer the ratio of propellant 12 to 114 to be in the range 2 to 1:1 and preferably 1.5:1 by weight, ie we prefer an excess of

Spropellant 12 over propellant 114.
The preferred dosages of active drug will be dependent on several factors including the particular azole antifungal agent used and the patient's diagnosis. However, when the treatment is to be used prophylactically. we prefer that adequate levels of the drug are maintained in the lung to prevent invasive fungal colonisation.

When the formulation is in the form of a non-pressurised dry powder, eg a capsule for inhalation, a unit dose of active ingredient may be from 0.05 to 40 mg,

0 more preferably 1 to 30 rg, particularly 5 to 20 mg.

When the formulation is in the form of a pressurised aerosol formulation, the aerosol dispensing pack is preferably provided with a valve adapted to deliver unit dosages of between 0.025 and 0.25mls, and preferably 0.05

5or O.lmls of composition. We prefer the valve to deliver 0.1, 1, 2, 3, 4 or 5mg of active ingredient and unit doses of these quantities of the drug are provided.

The pressurised aerosol formulations of the invention may be made by mixing the various components at a

0 temperature and pressure at which the propellant is in the liquid phase and the active ingredients are in the solid phase.

In producing the pressurised aerosol compositions and packages of the invention, a container equipped with a

25 valve is filled with a propellant containing the f inely divided active ingredient in suspension. A container may first.be charged with a weighed amount of dry active ingredients which have been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. A container may also be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in that component of the
propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. As a further alternative a bulk of the total composition may be made and portions of this bulk compositon may be filled into the container through the valve. Throughout the preparation of the product care is desirably exercised to minimise the absorption of moisture. on operating the valve, the powder will be dispensed in a stream of propellant which will vaporise providing an aerosol of dry powder.

It has.not previously been suggested that azole

)antifungals may be used as inhalation medicaments. As such finely divided powdered azole antifungal is novel. According to the invention, there is provided finely divided powdered azole antifungal with a mass median diameter in the range 0.1 to 10 microns. We prefer at

Sleast 95% of such powdered antifungal to have a mass median diameter in this range.

The compositions of the invention may be used in the remedial treatment or, more preferably, in the prophylaxis of fungal infections of the airways. The compositions of the invention, when administered via inhalation, will be particularly useful for the prophylaxis of systemic fungal infections whose portal of entry is the respiratory system.

According to a further aspect of the invention we provide a composition for the prophylaxis of fungal

0infections whose main portal of entry is the respiratory system.

The formulations of the invention are advantageous in that they are less toxic, more efficacious, give rise to fewer side effects are better tolerated or have other

5 useful properties compared to known therapies.

Asperaillus and cryptococcus are significant mycotic pathogens which enter the body via the lungs. The compositions of the invention may, therefore, be used for the prophylaxis and/or treatment of aspergillosis and

cryptococcosis. Patients particularly susceptible to invasive aspergillosis are those with defective neutrophil function and/or neutropenia, for example those with hematologic and lymphoreticular malignancy, organ transplants, or high dose steroid use. Some asthmatic

patients are also predisposed to allergic bronchopulmonary aspergillosis (ABPA) for which there is no established therapy. Treatment of the symptoms of asthma and/or MPA using steroids increases the risk of developing invasive disease. Patients particularly at risk of developing cryptococcosis are those with AIDS, lymphoreticular malignancies, organ transplants, chronic steroid use, sarcoidosis, chronic active hepatitis, connective tissue disorders or severe diabetes mellitus. The treatment may be administered by nasal inhalation; however we prefer oral inhalation.

The dosage to be given will clearly vary with the patient and with their condition. In general, however, relatively low doses administered at an interval to maintain adequate pulmonary drug concentration are indicated.

According to the invention there is also provided a method of prophylaxis of a fungal pulmonary infection, especially infections caused by aspergillosis or cryptococcosis, which comprises administering by inhalation a therapeutically effective amount of an azole antifungal agent

o a patient predisposed to such an infection.

Claims

Claims

1. A pharmaceutical formulation c , omprising, as active ingredient, an azole antifungal in a form suitable for administration by inhalation.
2. A pharmaceutical formulation according to claim 1, in the form of a dry powder.
3. A pharmaceutical formulation according to Claim 2 which contains a pharmaceutically acceptable liquefied gas aerosol propellant.

4. A pharmaceutical formulation according to Claim 3 which contains from 0.1 to 12% by weight of the active ingredient.

5. A pharmaceutical formulation according to Claim 3, wherein at least 95% by weight of the particles of active ingredient have a mass median diameter of from 0.1 to 10 microns.

6. A pharmaceutical formulation according to Claim 2 which is non-pressurised.

7. A pharmaceutical formulation according to Claim 6, wherein the active ingredient is in admixture with a pharmaceutically acceptable carrier. 8. A pharmaceutical formulation according to Claim 6, wherein at least 95% by weight of the particles of the active ingredient have a mass median diameter of from 0.1 tO 10 microns.

9. A pharmaceutical formulation according to claim 1, in the form of-an aqueous solution or suspension for use with a nebu-liser-device.

10. Finely divided powdered azole antifungal with a mass median diameter in the range 0.1 to 10 microns. T

11. A pharmaceutical formulation according to any one of Claims 1 to 8, wherein the azole antifungal is selected from clotrimazole, econazole nitrate, fluconazole, itraconazole, ketoconazole, miconazole nitrate and saperconazole.